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Shwachman-Diamond syndrome: diarrhea, no longer required?

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Abstract

Exocrine pancreatic insufficiency and diarrhea have been hallmarks in the diagnosis of Shwachman-Diamond Syndrome (SDS). We report two cases of genetically-confirmed SDS in patients who presented with an unusual phenotype. Patient #1 presented with pancytopenia without other system involvement, while patient #2 presented with severe neutropenia, anemia, and a bifid thumb. Neither patient had diarrhea or malabsorption. Both patients had the classic heterozygous mutations c183_184 TA>CT and c.258+2 T>C in the SBDS gene. Incomplete phenotypes may be more common than previously recognized in bone marrow failure syndromes; gastrointestinal symptoms should not be considered a prerequisite for SDS.

Keywords

Shwachman-Diamond syndrome; neutropenia; diarrhea; exocrine pancreatic insufficiency

Introduction

Shwachman-Diamond syndrome (SDS) has been classically described by the triad of bone marrow failure, exocrine pancreatic insufficiency, and skeletal abnormalities [1]. Skeletal dysplasia, immunologic abnormalities, cardiac defects, hepatic dysfunction, and neuropsychological impairment may also occur [2-3]. The majority of patients have biallelic mutations in the Shwachman-Bodian-Diamond syndrome (SBDS) gene on chromosome 7 [4]. The highly evolutionarily-conserved SBDS gene produces the SBDS protein, which is expressed ubiquitously [5]. Studies on the yeast ortholog as well as human cells from patients with SDS provide strong evidence that the SBDS protein co-localizes to ribosomes

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in the nucleoli and cytoplasm and is involved in ribosome biogenesis and function [2,4-7]. The tissue expression patterns of the SBDS protein and its association with ribosomal protein production likely underlie the multi-organ involvement of the syndrome.

Pancreatic exocrine insufficiency has been long established as a hallmark feature of SDS patients, although its severity varies [1-2]. Infants typically present with multiple gastrointestinal symptoms, including diarrhea, steatorrhea, height <3rd percentile, failure to thrive, or fat-soluble vitamin deficiencies [1-2]. Pancreatic insufficiency is confirmed through the measurement of serum trypsinogen (patients <3 years), serum isoamylase (patients >3 years), fecal elastase, or 72-hour fecal fat [2,8]. Imaging of the pancreas by ultrasound/MRI may reveal fatty infiltration [9]. We report two cases of genetically-confirmed SDS that presented in the first three years of life without any gastrointestinal symptoms.

Case Reports

Patient #1 is a 3 year-old Hispanic male who presented with epistaxis. He had no history of severe infections. His weight and height were at the 25th percentile for age. CBC revealed WBC $2.52 \times 10^3/\mu\text{L}$ (3% monocytes, 37% neutrophils, 59% lymphocytes; absolute neutrophil count $935/\mu\text{L}$), Hgb 7.6 g/dL, MCV 68 fL, platelets $85 \times 10^3/\mu\text{L}$, and reticulocyte count 1.1%. ALT/AST were elevated (235/257 U/L). Serum iron and ferritin were low, presumably due to epistaxis. A bone marrow aspirate revealed erythroid hyperplasia, myeloid hypoplasia, and dysplastic megakaryopoiesis. Over the next year, he had persistently stable pancytopenia (see **Figure 1**), but was clinically well. He continued to grow without episodes of diarrhea. Specific pancreatic exocrine function was not tested. Amylase and lipase were normal (13 and 15 U/L, respectively). CT scan revealed a normal appearing pancreas. A repeat bone marrow showed trilineage dysplasia and a clonal cytogenetic abnormality of deletion 20q. Testing was performed for Fanconi anemia, AML1-Runx 1 mutation, dyskeratosis congenita, and SDS. Genetic testing revealed bi-allelic mutations in the SBDS gene: c183_184 TA>CT and c.258+2 T>C. A follow-up bone marrow 3 months later showed decreased cellularity (40%) and persistent trilineage dysplasia with 3% blasts. Based on evidence of dysplasia with a persistent clonal cytogenetic abnormality, the patient underwent a matched (10:10) unrelated donor peripheral blood stem cell transplant 16 months after presentation with the following conditioning regimen: busulfan (3.2 mg/kg/dose to achieve an area under the curve concentration of 3800-4200 l/mol/min)/fludarabine (30 mg/m²/day $\times$ 6)/anti-thymocyte globulin (2 mg/kg/d $\times$ 4)/low dose total body irradiation (400 cGy). He developed grade II acute graft-versus-host disease (GVHD) of the skin, treated with prednisone, but he has not developed chronic GVHD. Bone marrows performed on Days +112 and +264 showed trilineage hematopoiesis and normal cytogenetics. Follow-up for SBDS mutation testing from the peripheral blood remains negative at 2.5 years after diagnosis and 2 years post transplant.

Patient #2 is an Asian-Indian male who presented at 3 months of age with fevers. Physical exam revealed a right bifid thumb and a well-appearing male, with weight and height at the 25th percentile for age. Family history was unremarkable and there was no known consanguinity. CBC revealed WBC $10.6 \times 10^3/\mu\text{L}$ (1% neutrophils, 1% bands, 98% lymphocytes; absolute neutrophil count $106/\mu\text{L}$), Hgb 5.9 g/dL, MCV 84 fL, Plt $594 \times 10^3/\mu\text{L}$. Liver function tests were elevated (145/156 U/L). He has never had a history of diarrhea or malabsorption, though he did have a fecal elastase that was low (<15 g pancreatic elastase/g stool, normal >200 g pancreatic elastase/g stool). Trypsinogen was also low (<1.2 ng/ml, normal 10.0-57.0 ng/ml). Testing of vitamin A, D, E, and K revealed normal levels (Vitamin A 32 mcg/dl, normal 20-43 mcg/dl; 1,25-hydroxy Vitamin D 29.7 pg/ml, normal 15-80 pg/ml; Vitamin E 3.2 mcg/dl, normal 2.9-16.6 mcg/dl; Vitamin K 188 g/ml, normal 88-1160). Bone

marrow aspirate showed erythroid hypoplasia, myeloid arrest at the myelocyte/promyelocyte stage, no evidence of leukemia or dysplastic changes, and normal cytogenetics. Testing was performed for the following disorders: Fanconi anemia, cyclic neutropenia, severe congenital neutropenia (ELA2 and HAX1), and SDS. Genetic testing revealed bi-allelic mutations in the SBDS gene: c183_184 TA>CT and c.258+2 T>C. The patient also had a heterozygous codon repeat mutation in the HAX1 gene, which is of unknown significance. He required 3 transfusions of packed red blood cells prior to age 6 months, though has not required any since and has maintained hemoglobins >9 g/dl. At diagnosis, the patient's neutropenia exhibited a cyclic pattern, achieving an ANC>500 cells/uL approximately once every 28 days (see **figure 2**). He had one episode of sepsis that resulted in a brief hospitalization for IV antibiotics. At age 6 months, he was started on filgrastim and has been maintained on <2 mcg/kg/day without any further infections. He has been growing normally without pancreatic enzyme supplementation, maintaining 25%ile for weight and height, and developing normally now at age 3 years.

Discussion

We have identified two SDS patients without any gastrointestinal symptoms. Heterogeneity of phenotype is classic in SDS; still, the vast majority of reported cases have significant gastrointestinal symptoms. Hashmi et al found pancreatic dysfunction to be the most common non-hematologic manifestation of SDS, with 85% of patients affected, with the majority requiring treatment with enzymes/vitamins [10]. Ip et al documented extremely high sensitivity for serum trypsinogen (96%) and serum isoamylase (100%) among patients with SDS less than 3 years of age [8]. Patient #2 clearly had laboratory evidence of exocrine pancreatic dysfunction, yet he did not have overt symptoms. Patient #1 was diagnosed with SDS prior to pancreatic testing.

Linden et al reported a 6 year old female without clinical evidence of pancreatic insufficiency, though that patient did have decreased fecal elastase [11]. With the advent of genetic testing and increased awareness of SDS, we suspect there may be additional cases without clinical evidence of malabsorption.

Genotype-phenotype correlation has not yet been defined for patients with SDS. Less than 100% of patients meeting the diagnostic criteria for SDS will have a detectable mutation at the SBDS gene. In three recent comprehensive reports, 81% (25/31), 89% (141/158), and 91% (20/22) of patients with SDS did have bi-allelic mutations [4,10,12]. Both of our patients have the classic compound heterozygous mutations c183_184 TA>CT and c.258+2 T>C in the SBDS gene on chromosome 7. This exact two allele combination is seen in the majority of patients with SDS: 50% (79/158) of patients in one review and 73% (16/22) in another [4,12]. Further, additional mutation combinations almost always include one of those two alleles. Duplications often result from isochromosome 7 [13]. The c183_184 TA>CT nonsense mutation produces a truncated protein and results in complete loss of the SBDS protein. Homozygotes for that mutation have not been identified as this likely results in lethality [2]. The c.258+2 T>C mutation results in alternative splicing and produces a small amount of functional protein [6]. Minelli et al have hypothesized that patients homozygous for the c.258+2 T>C mutation may have a milder phenotype and a lower incidence of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) [13] in comparison to the majority of patients with SDS who have a marked increased risk of leukemic development. Still, even the subset of lower risk patients homozygous for the c. 258+2 T>C mutation may have a higher risk of MDS/AML than the general population [13]. Genetic mutation differences associated with non-hematologic manifestations have not been described. Recently, Hashmi et al reviewed the genotype-phenotype comparisons for all patients with SDS on a Canadian registry [10]. They found that classic patients with SBDS

bi-allelic mutations were significantly more likely to have pancreatic dysfunction, yet significantly less likely to have severe marrow failure in comparison to SDS patients without genetic mutations [10].

Of unknown pathophysiologic significance, patient #2 has a single, heterozygous codon repeat at HAX1 in addition to compound heterozygous mutations in SBDS. This patient had very severe neutropenia, with neutrophil counts typically below 200 in the absence of G-CSF. HAX1 is a known cause for autosomal recessive severe congenital neutropenia. Like SBDS, HAX1 is ubiquitously expressed and has roles in cell migration and apoptosis [14]. This genetic combination of abnormalities in SBDS and HAX1 has not been previously described, and the impact of the single HAX1 allele mutation in the setting of SBDS remains unknown. Patient #2 also exhibited a cyclic pattern of neutropenia, which has been rarely described previously in SDS [15]. However, our patient's cyclic pattern was not typical of the classic cyclic neutropenia diagnosis, as our patient had longer duration of nadir neutropenia with each cycle as well as longer cycles than would be seen in cyclic neutropenia.

Timely diagnosis is important for patients with SDS for multiple reasons. First, if patients have evidence of pancreatic insufficiency, their nutritional/vitamin status can be maximized. All patients are recommended to have fat soluble vitamin measurements and consult with a pediatric gastroenterologist, because many patients may require vitamin ADEK replacement [16]. Pancreatic exocrine insufficiency improves as patients age in 50% of patients with SDS [1-2]. Second, there is a significant risk of progression to MDS/AML, estimated to be at least 36% at 30 years [2,17]. Interestingly, there may be a male predominance to those SDS patients who develop MDS/AML: 92% of reported patients were male [18].

Due to the risk of leukemic progression, allogeneic stem cell transplantation has emerged as a consideration for these patients, with improved outcomes with transplantation prior to the development of MDS/AML. Initial transplantation with myeloablative conditioning led to greater than expected toxicity, with post-transplant overall survival rates of only 60-65% [19-20]. Consequently, reduced-intensity conditioning has been shown to be effective for SDS patients. Bhatla et al used an alemtuzumab/fludarabine/melphalan regimen with success in 7 patients with SDS who remain alive at a median of 18 months post transplant [21]. Our patient #1 tolerated a busulfan/fludarabine/low dose TBI regimen extremely well.

Defective ribosome biogenesis and the associated organ-specific response to cellular stress may underlie the variability of multi-system disease of Shwachman-Diamond syndrome. Incomplete phenotypes may be more common than previously recognized in bone marrow failure syndromes. Gastrointestinal symptoms, known to be highly variable, are not necessary to make the diagnosis of SDS as evidenced by our two patients and review of the literature. SDS should be strongly considered for any patient with persistent neutropenia/marrow failure, even in the absence of gastrointestinal symptoms.

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References

1. Dror Y. Shwachman-Diamond syndrome. *Pediatr Blood Cancer*. 2005; 45(7):892–901. [PubMed: 16047374]
2. Burroughs L, Woolfrey A, Shimamura A. Shwachman-Diamond syndrome: a review of the clinical presentation, molecular pathogenesis, diagnosis, and treatment. *Hematol Oncol Clin North Am*. 2009; 23(2):233–248. [PubMed: 19327581]

3. Kerr EN, Ellis L, Dupuis A, et al. The behavioral phenotype of school-age children with shwachman diamond syndrome indicates neurocognitive dysfunction with loss of Shwachman-Bodian-Diamond syndrome gene function. *J Pediatr*. 2010; 156(3):433–438. [PubMed: 19906387]
4. Boocock GR, Morrison JA, Popovic M, et al. Mutations in SBDS are associated with Shwachman-Diamond syndrome. *Nat Genet*. 2003; 33(1):97–101. [PubMed: 12496757]
5. Ganapathi KA, Austin KM, Lee CS, et al. The human Shwachman-Diamond syndrome protein, SBDS, associates with ribosomal RNA. *Blood*. 2007; 110(5):1458–1465. [PubMed: 17475909]
6. Austin KM, Leary RJ, Shimamura A. The Shwachman-Diamond SBDS protein localizes to the nucleolus. *Blood*. 2005; 106(4):1253–1258. [PubMed: 15860664]
7. Finch AJ, Hilcenko C, Basse N, et al. Uncoupling of GTP hydrolysis from eIF6 release on the ribosome causes Shwachman-Diamond syndrome. *Genes Dev*. 2011; 25(9):917–929. [PubMed: 21536732]
8. Ip WF, Dupuis A, Ellis L, et al. Serum pancreatic enzymes define the pancreatic phenotype in patients with Shwachman-Diamond syndrome. *J Pediatr*. 2002; 141(2):259–265. [PubMed: 12183724]
9. Toiviainen-Salo S, Raade M, Durie PR, et al. Magnetic resonance imaging findings of the pancreas in patients with Shwachman-Diamond syndrome and mutations in the SBDS gene. *J Pediatr*. 2008; 152(3):434–436. [PubMed: 18280855]
10. Hashmi SK, Allen C, Klaassen R, et al. Comparative analysis of Shwachman-Diamond syndrome to other inherited bone marrow failure syndromes and genotype-phenotype correlation. *Clin Genet*. 2010
11. Linden T, Ehlert K, Niemeyer CM, et al. Molecular diagnosis of Shwachman-Diamond syndrome in a child with incomplete clinical disease phenotype. *Pediatr Blood Cancer*. 2010; 55(1):177–179. [PubMed: 20486183]
12. Maserati E, Pressato B, Valli R, et al. The route to development of myelodysplastic syndrome/acute myeloid leukaemia in Shwachman-Diamond syndrome: the role of ageing, karyotype instability, and acquired chromosome anomalies. *Br J Haematol*. 2009; 145(2):190–197. [PubMed: 19222471]
13. Minelli A, Maserati E, Nicolis E, et al. The isochromosome i(7)(q10) carrying c.258+2t>c mutation of the SBDS gene does not promote development of myeloid malignancies in patients with Shwachman syndrome. *Leukemia*. 2009; 23(4):708–711. [PubMed: 19148133]
14. Fadeel B, Grzybowska E. HAX-1: a multifunctional protein with emerging roles in human disease. *Biochim Biophys Acta*. 2009; 1790(10):1139–1148. [PubMed: 19524642]
15. Dokal I, Rule S, Chen F, et al. Adult onset of acute myeloid leukaemia (M6) in patients with Shwachman-Diamond syndrome. *Br J Haematol*. 1997; 99(1):171–173. [PubMed: 9359520]
16. Rothbaum R, Perrault J, Vlachos A, et al. Shwachman-Diamond syndrome: report from an international conference. *J Pediatr*. 2002; 141(2):266–270. [PubMed: 12183725]
17. Donadieu J, Leblanc T, Bader Meunier B, et al. Analysis of risk factors for myelodysplasias, leukemias and death from infection among patients with congenital neutropenia. Experience of the French Severe Chronic Neutropenia Study Group. *Haematologica*. 2005; 90(1):45–53. [PubMed: 15642668]
18. Shimamura A. Shwachman-Diamond syndrome. *Semin Hematol*. 2006; 43(3):178–188. [PubMed: 16822460]
19. Donadieu J, Michel G, Merlin E, et al. Hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: experience of the French neutropenia registry. *Bone Marrow Transplant*. 2005; 36(9):787–792. [PubMed: 16151425]
20. Cesaro S, Oneto R, Messina C, et al. Haematopoietic stem cell transplantation for Shwachman-Diamond disease: a study from the European Group for blood and marrow transplantation. *Br J Haematol*. 2005; 131(2):231–236. [PubMed: 16197455]
21. Bhatla D, Davies SM, Shenoy S, et al. Reduced-intensity conditioning is effective and safe for transplantation of patients with Shwachman-Diamond syndrome. *Bone Marrow Transplant*. 2008; 42(3):159–165. [PubMed: 18500373]

Figure 1.
Absolute neutrophil counts of patient #1 from presentation through stem cell transplant.

Figure 2.
 Absolute neutrophil and monocyte counts of patient #2 from initial presentation.